REMARKS

Claims 1, 3, 7, 8, 10-13 and 17 will be pending upon entry of the presently made amendments.

Claims 4-6, 9, 14-16 and 18-25 have been canceled without prejudice.

Claim 1 has been amended without prejudice to recite that the cancer is treatable by the inhibition of JNK and at least one other protein kinase. Support for this amendment is found in the specification as filed at least at page 14, lines 3-6 and page 43, lines 11-19.

Claim 1 has been further amended without prejudice to recite particular groups in the definitions of variables R_3 and R_4. Support for these amendments is found in the specification as filed at least at page 15, lines 12-22.

Claims 1 and 13 have been amended without prejudice to replace the term "modulated" with "inhibited." Support for these amendments is found in the specification as filed at least at page 19, lines 19-21.

Claim 13 has been further amended without prejudice to recite that the activity of JNK is selectively inhibited over other kinases. Support for this amendment is found in the specification as filed at least at page 42, lines 24-28.

Claims 10 and 17 have been amended without prejudice to depend from claim 1.

Claim 11 has been amended without prejudice to clarify that "other" protein kinases are recited therein.

No new matter has been added.

Applicants reserve the right to prosecute the subject matter of any amended, canceled or withdrawn claim or any unclaimed subject matter in one or more related applications.

I. The Rejection of Claims 1-3, 5 and 7-17 Under 35 U.S.C. 112, First Paragraph

Claims 1, 3, 5 and 7-17 remain rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. In particular, the Examiner has stated that the specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse this rejection.

In response to Applicants' arguments, the Examiner has noted that Force *et al.* states that compounds showing high activity and specificity *in vitro* may show markedly different and even unexpectedly nonspecific activity *in vivo*. In addition, while acknowledging that Manning *et al.* teaches a role of JNK in cancer, the Examiner has stated that Manning *et al.* does not teach that every modulator of JNK activity will treat all cancers.

Preliminarily, Applicants note that the claims have been amended to recite methods for treating cancer treatable by the inhibition of JNK and at least one other protein kinase. In other words, the pending claims are not directed to the treatment of *all* cancers, but are instead directed to the treatment of a focused subset of cancers that are treatable by the inhibition of JNK and at least one other protein kinase. In addition, the claims are not directed to every modulator of JNK activity, but instead recite a focused class of chemical compounds with a well-defined core structure.

Nevertheless, Applicants again respectfully submit that the possibility that some compounds within the scope of the class of compounds recited in the pending claims may not be effective *in vivo* does not preclude patentability. *Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1004) ("Testing for full safety and effectiveness...is more properly left to the [FDA]"); *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564 (Fed. Cir. 1996) ("Of course, it is possible that some compounds active *in vitro* may not be active *in vivo*).

Applicants respectfully point the Examiner to the decision in *In re Bundy* wherein the United States Court of Customs and Patent Appeals held that all that is necessary to satisfy the how-to-use (*i.e.*, enablement) requirement of 35 U.S.C. § 112 is the disclosure of some activity coupled with the knowledge as to the use of this activity. *In re Bundy*, 642 F.2d 430, 434 (C.C.P.A. 1981). In particular, the Court held that claims can be enabled notwithstanding the absence of examples of dosages for human use or animal tests. *Id.* (held that applicant's disclosure that novel prostaglandins had certain pharmacological properties and possessed activity similar to known prostaglandins was sufficient to enable one skilled in the art). In explaining its reasoning, the Court stated that the early filing of an application with its disclosure of novel compounds which possess significant therapeutic use is to be encouraged. *Id.* The Court further stated that specific testing of thousands of compounds...in order to satisfy 35 U.S.C. § 112 would delay disclosure and frustrate, rather than further, the interests of the public and noted that one skilled in the art would know how to use the compounds to determine the specific dosages for the various biological purposes. *Id.*

Accordingly, Applicants respectfully submit that the claims are enabled because the specification teaches compounds that have activity against multiple kinases, provides assays for measuring the activity of compounds against numerous kinases and further provides a nexus between kinase inhibition and the treatment of cancer (which is further evidenced by the previously provided peer-reviewed publications by Force *et al.* and Manning *et al.*).

Regarding the Examiner's statement with respect to the "speculative" and "sufficiently unusual" nature of the claimed use, Applicants respectfully submit that the Federal Circuit has specifically stated that the treatment of cancer with chemical compounds does not suggest an unbelievable undertaking or involve implausible scientific principles. *In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1995).

The Examiner has further alleged that undue experimentation would be required for one skilled in the art to practice the claimed invention. In particular, the Examiner has stated that one would have to determine a useful model that correlates with clinical efficacy, a dosage range and a route of administration. As the Examiner is aware, experimentation is not necessarily undue because it is complex, time consuming or expensive. *United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988) (studies costing $50,000 and taking 6-12 months to complete failed to show undue experimentation); M.P.E.P. § 2164.06. With respect to the availability of a useful model that correlates with clinical efficacy, Applicants respectfully submit that such models are well known in the art and that it is well established that the specification need not teach, and preferably omits, what is well known in the art. *Hybritech Inc. v. Monoclonal Antibodies*, 802 F.2d 1367,1385 (Fed. Cir. 1986).

The Examiner has further stated that if the model, dosage range or route of administration failed, one would have to start over again to determine suitable methods, dosage ranges and routes of administration in which to determine if the compounds will work to treat cancer. Applicants respectfully submit that such is the nature of experimentation and it has been held that requiring disclosure which would enable one skilled in the art to determine an outcome, with reasonable certainty before performing the experiment would result in all experimentation being "undue," since the term "experimentation" implies that the success of the particular activity is uncertain. *Application of Angstadt*, 537 F.2d 498, 503 (C.C.P.A. 1976). Furthermore, the Federal Circuit has held that a specification is enabling in part because those skilled in the art would know how to conduct a dose response study to determine the appropriate amounts to be used. *Merck & Co., Inc. v. Biocraft Laboratories, Inc.*, 874 F.2d 804, 809 (Fed. Cir. 1989).

In summary, Applicants submit that the disclosure of the present application, in combination with what is known in the art regarding small molecule kinase inhibitors, satisfies the enablement requirement of 35 U.S.C. § 112, first paragraph. Specifically, the present application provides small molecule kinase inhibitors (wherein the Examiner has acknowledged that the specification is enabling for determining the activity of various indazole compounds that inhibit, modulate or regulate tyrosine kinase signal transduction)

and the literature demonstrates not only that kinases are accepted therapeutic targets for cancer, but that a significant number of clinical trials directed to the use of small molecule kinase inhibitors as anti-cancer agents are currently ongoing. Thus, it is within the means of those skilled in the art to practice the present claims without undue experimentation.

Claims 5, 9, 14 and 16 have been canceled without prejudice.

Accordingly, Applicants respectfully submit that the rejection of claims 1, 3, 5 and 7-17 under 35 U.S.C. § 112, first paragraph, has been overcome and should be withdrawn.

II. The Rejection of Claims 1-3, 5 and 7-17 Under 35 U.S.C. 112, First Paragraph

Claims 1, 3, 5 and 7-17 remain rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. In particular, while acknowledging that the specification is enabling for determining the activity of various indazole compounds that inhibit, modulate or regulate tyrosine kinase signal transduction, the Examiner has stated that it does not reasonably provide enablement for the treatment of all cancers with the indazole compounds.

As discussed above, Applicants note that the pending claims do not recite the treatment of all cancers. Rather, the claims as amended recite the treatment of cancer treatable by the inhibition of JNK and at least one other protein kinase.

Accordingly, for the same reasons set forth above, Applicants respectfully submit that the rejection of claims 1, 3, 5 and 7-17 under 35 U.S.C. § 112, first paragraph, has been overcome and should be withdrawn.

III. Advisory Action

In the Advisory Action mailed on September 23, 2008 in connection with the present application, the Examiner has pointed to MPEP § 2164.02 as teaching that a "'working example' between an *in vitro* or *in vivo* animal model assay must correlate with the claimed method invention" and has argued that the working examples of the present application do not correlate with the claimed methods.

In particular, the Examiner stated that there is no teaching that the *in vitro* assays correlate to treating cancer *in vivo*. Applicants respectfully submit that the Examiner has improperly shifted the burden with respect to evidence of the correlation of the models provided by the present application and the claimed methods. As stated in MPEP § 2164, the initial burden is on the examiner to give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. Applicants respectfully submit that no such evidence has been provided by the Examiner.

Nevertheless, Applicants respectfully submit that the teachings of Force *et al.* and Manning *et al.* do, in fact, teach a correlation between the models provided by the present application and the claimed methods. MPEP § 2164.02 states that if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Notably, MPEP § 2164.02 clearly states that a "rigorous" or an "invariable exact correlation" is not required (citing *Cross v. Iizuka*, 753 F.2d 1040, 1050 (Fed. Cir. 1985)). Applicants respectfully submit that as taught by both Force *et al.* and Manning *et al.*, the art is such that a correlation between *in vitro* kinase (*e.g.*, JNK) inhibition and the treatment of cancer is well recognized. Otherwise, pharmaceutical companies would not be investing substantial resources into screening compounds for kinase inhibition activity as part of the drug discovery process for anti-cancer agents.

Specifically, Force states that the pathophysiological dysfunction of protein kinase signaling pathways underlies the molecular basis of many cancers (*see* Abstract) and even predicts that in the future, cancers will be defined not only by tumor type and stage but also by the protein kinase activity profile (*i.e.*, which kinases are dysregulated) (*see* page 1197, first column, lines 34-38). Force further provides and extensive list of small molecule kinase inhibitors at pages 1198-1199 which have either successfully completed or are currently in human clinical trials.

Manning discusses the evidence supporting the application of JNK inhibitors to treat *inter alia* oncological disease in humans (*see* page 554, last line of abstract). Regarding cancer, Manning summarizes the data pointing to the link between JNK activity and a wide variety of cancers (*e.g.*, pancreas, lung, breast, colon and prostate) and suggests that JNK could play more than one role in tumour development (*see*, "Cancer" at pages 561-562).

Thus, Applicants respectfully submit that in view of the lack of evidence by the Examiner of non-correlation, further in view of the teaching by Force *et al.* and Manning *et al.* of a correlation between such models and the claimed methods, the specification does provide working examples that support the enablement of the pending claims.

IV. Provisional Double Patenting

Claims 1, 3 and 14-17 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being allegedly unpatentable over claims 1-2 and 9-10 of co-pending U.S. Application No. 11/512,836 (the "'836 application") and claims 1-14 of co-pending U.S. Application No. 11/376,786 (the "'786 application"). Per M.P.E.P § 804, a provisional double patenting rejection should continue to be made unless it is the sole

remaining rejection in one of the applications. Upon entry of the presently made amendment and remarks, Applicants believe that the sole remaining rejections in the present application will be the provisional double patenting rejections over the `836 and `786 applications. Applicants will consider filing a terminal disclaimer in connection with the `836 and `786 applications upon indication of allowable subject matter in the present application. Accordingly, Applicants respectfully request that the provisional double patenting rejection over the `836 and `786 applications be withdrawn.

CONCLUSION

Applicant respectfully requests that the above remarks be entered in the present application file. No fee is believed to be due in connection with this Response other than that due in connection with the Request for Continued Examination; however, in the event that any additional fee is due, please charge the required fee to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

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